Exhibit C

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	**Master File No. 2:12-MD-02327** **MDL 2327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**
THIS DOCUMENT RELATES TO: *Wave 4 Cases*	

EXPERT REPORT OF NICOLE B. FLEISCHMANN, M.D.

EXPERT REPORT OF NICOLE B. FLEISCHMANN, M.D.

(TVT Retropubic, MDL General Report)

I have prepared this Expert Report in the matter of In re: Ethicon, Inc. Pelvic Repair System Products Liability Litigation, MDL No. 2327, currently pending in the United States District Court for the Southern District of West Virginia, before the Hon. Joseph R. Goodwin. My opinions set forth in this report are made to a reasonable degree of medical certainty, and are based on information and knowledge I have acquired from my education, training, personal experience in private practice, teaching, discussion and interaction with other pelvic surgeons in professional activities and conferences, research and review of medical literature and records.

QUALIFICATIONS

I am a practicing urologist with subspecialty training in Female Pelvic Medicine and Reconstructive Surgery (FPMRS). I have board certification both in Urology and in FPMRS, a new board certification with the American Board of Urology (ABU) and the American Board of OB/GYN (ABOG). Following my graduation from medical school and my residencies in surgery and in urology, I completed a fellowship in Female Urology and Voiding Dysfunction at the New York University School of Medicine. After my fellowship, I served on the faculty at Mount Sinai School of Medicine in New York City, as Director of Female Urology and Voiding Dysfunction. Since then, I have had a busy clinical practice at Westchester Urological Associates, a division of Advanced Urology in White Plains, New York, where I treat almost exclusively women with urologic issues such as incontinence, pelvic organ prolapse, recurrent urinary tract infections, hematuria and kidney stones. In addition to my private practice at White Plains Hospital, I am very involved in the training of residents (Urology and Gynecology) and

fellows through my responsibilities as the Associate Fellowship Director of FPMRS and Associate Clinical Professor of Urology and Ob/Gyn at Albert Einstein College of Medicine in Bronx, NY. I run a clinic, didactic sessions and perform surgery at the teaching hospital once a week. My credentials are further set forth in my *curriculum vitae*, which is Exhibit A to this Report.

On a daily basis, I diagnose and treat women with urinary incontinence, a debilitating condition which affects millions of women around the world. I take great pleasure in working to eliminate this problem for women and improving their overall quality of life, through both surgical and non-surgical treatment. For at least two or three days of the week, I perform and train others to perform surgical procedures to correct stress urinary incontinence. The most common procedure that I do is the midurethral sling. Over the years, I have placed roughly 1500 slings, the overwhelming majority of which are the Gynecare Tension Free Support for Incontinence (TVT) in both retropubic and obturator (TVT-O) approaches. In addition, I perform other types of anti-incontinence procedures such as autologous fascial slings and Burch colposuspensions on a routine basis. I also do many procedures for pelvic organ prolapse including transvaginal mesh repairs and robotic sacral colpopexy using Y-mesh. Based on Ethicon's records, I attended an Ethicon-sponsored Professional Education event for TVT in 2002 (and a Prolift preceptorship and proctorship in 2006 and 2007, respectively), but the bulk of my training on TVT was in my Fellowship at NYU and subsequently in my clinical practice.

MATERIALS I HAVE REVIEWED

In the course of preparing this report, I have reviewed numerous documents. I have examined the published literature on TVT. I have reviewed professional education materials

produced by Ethicon, as well as the Instructions for Use (IFU) of the TVT Retropubic product, TVT patient brochures, and the TVT Surgeon Resource Monograph. I have also read the numerous medical society statements and the statement issued by the Food and Drug Administration (FDA) regarding synthetic midurethral slings. A complete list of the materials that I have reviewed is attached as Exhibit B to this Report, and will be supplemented as I review more materials.

URINARY INCONTINENCE

Urinary incontinence (UI), a debilitating medical condition that affects millions of women, is defined as the involuntary loss of urine. According to Nygaard et al (Jama, 2008) approximately 15.7% of women suffer from urinary incontinence or 12 million US adults. One study (Wu, et al. 2009 JOBGYN) forecasts that as the population ages, by 2050 there will be a public health crisis with over 48 million American women affected. The annual direct cost of urinary incontinence in the United States (in 1995 dollars) was estimated as $16.3 billion (Wilson et al. Obstet Gynecol. 2001).

Urinary incontinence has both a physical and emotional impact on a woman's quality of life. Physical complications include skin problems such as skin infections and sores from constantly wet skin as well as recurrent urinary tract infections. UI can affect one's overall physical health by impairing the ability to exercise or be generally active for fear of increasing leakage episodes. Because UI may cause social isolation, loss of sexual function, and other psychosocial problems, it could have significant impact on patients' emotional well-being. Studies have shown that patients suffering with UI are more depressed, psychologically distressed, emotionally disturbed and socially isolated. (Zorn et al. JUROL 1999.) Moreover,

compared with continent individuals, those patients with UI also have higher levels of anxiety, lower quality of life scores, and poorer life satisfaction (Melvile 2002 Am. J. Obstet. Gynecology). As a result, urinary incontinence has an adverse effect on patients' daily lives, which can be devastating in the more extreme cases, and can become a barrier for normal social function.

Types of Urinary Incontinence

Urinary incontinence is divided into two subtypes: stress urinary incontinence (SUI) and urge urinary incontinence (UUI). People who have both subtypes have mixed urinary incontinence (MUI). SUI is defined as urine loss during periods of activity such as coughing, sneezing, lifting and exercise. The mechanism of urine loss is either weakened tissue support to the opening of the bladder (urethral hypermobility) or deficiency of the closure mechanism that holds urine inside the bladder (intrinsic sphincter deficiency), resulting in leakage of urine during periods of physical stress to the bladder. The amount of leakage can vary from a few drops to a significant volume. The most common reason for someone to have SUI is after a vaginal delivery, but other risk factors such as smoking, aging and genetics can all play a role.

Urge urinary incontinence is the involuntary loss of urine which is accompanied by or preceded by a strong urge. It is the inability to defer urinating in order to make it to the bathroom. The volume of urine loss can be large, causing extreme embarrassment. This condition can affect people of all ages, but is most common in the postmenopausal woman. Certain neurologic conditions such as cerebral vascular accidents, Parkinson's disease and multiple sclerosis can result in UUI. Another condition which leads to UUI is bladder outlet obstruction, which is when the bladder becomes irritated because it is unable to empty freely

such as in the case of men with enlarged prostates. As previously stated, people who have symptoms of both UUI and SUI are said to have mixed urinary incontinence, but typically, one of the subtypes is the prevailing problem.

Diagnosis of Incontinence

The treatments for UUI and SUI are different, so it is important that the clinician comes to the correct diagnosis before initiating a therapy. Most physicians will use a variety of tools to assess the type of incontinence. The first step is to acquire an accurate and thorough history from the patient. This can be accomplished through filling out questionnaires and an interview. Most women will be able to describe the circumstances in which they leak, and this is an invaluable piece of information to the clinician. It is also helpful to identify other medical conditions the patient suffers from, medications she takes, previous surgeries she has undergone, and family history. In the course of the interview, the physician should learn about the everyday life of the patient: what she does for a living, what her personal life is like, especially with regards to sexual activity, as all this information can be helpful when diagnosing and formulating a treatment plan.

The physical examination is also crucial to diagnosing the type of incontinence. In many cases, urine leakage can be elicited in women with SUI by simply asking them to cough or bear down during a pelvic examination. In addition, it is important to note any defects in the vaginal wall that may coexist with urinary incontinence such as cystocele, rectocele or uterine prolapse. Prolapse is a condition in which the pelvic organs herniate into the vagina and may or may not be accompanied by urinary incontinence. Other helpful information includes a post void residual test (PVR) in which the amount of urine left behind after a woman urinates is measured either by

sonogram or catheter drainage. A urinalysis and urine culture determines when a urinary tract infection is present or when there is the presence of blood in the urine, which may indicate another problem such as bladder cancer. When indicated, clinicians may ask patients to keep a voiding diary to log the amount they drink, how often they urinate and how many leakage episodes they have in a 24 hour period.

Urodynamic testing can be an extremely helpful tool in diagnosing incontinence conditions. It is a procedure by which the physician is able to demonstrate the exact cause of incontinence by reproducing the episode in a controlled setting. The test involves placing a small catheter in the bladder and another in the rectum or vagina. The catheter monitors pressure as the bladder fills with water. The physician is able to assess the capacity of the bladder, whether there are any involuntary bladder contractions during the filling process, whether the patient leaks with a cough and at what volume and pressure, and whether the voiding episode is normal and unobstructed. In some cases, the physician will look inside the bladder with cystoscopy to assess whether there are any abnormalities which could cause urine leakage such as a bladder stone or foreign body.

Treatment of Urge Urinary Incontinence

If the etiology of the incontinence is determined to be urgency incontinence, a conservative approach is usually offered in the form of behavioral management. Monitoring quantity and quality of fluid ingested, decreasing bladder irritants such as coffee and alcohol, performing kegels or pelvic floor exercises, and practicing timed voiding (going to the bathroom by the clock instead of waiting to the urge to arise) all fall under this category. Behavior therapy

can be very useful in mild forms of incontinence, but tends to be less effective as symptoms become more severe.

A helpful adjunct to behavioral therapy in OAB is medication. The most common drugs available are antimuscarinics which decrease unwanted urge symptoms and increase the functional bladder capacity. Currently available medications in this category are oxybutynin (Ditropan), tolteridine (Detrol), trospium (Sanctura), solifenicin (Vesicare), darifecinin (Enablex), Gelnique and the Oxytrol patch. The most common side effects of this class of medication are dry mouth, constipation, blurry vision and reflux. In 2012, mirabegron (Myrbetriq) was approved for use in overactive bladder – with a different mechanism of action and side effect profile.

Second line treatments for urge incontinence or overactive bladder are offered when medications are not effective or the side effects make them intolerable. BOTOX® (onabotulinumtoxinA) intravesical injection was recently FDA approved for both neurogenic and idiopathic overactive bladder. InterStim therapy or sacral nerve modulation is an implantable device which delivers a continuous low level electrical impulse to the nerves of the pelvis to help with bladder control. Both of these procedures can be performed either in the office or the operating room under local anesthesia.

As with any procedure, even minimally invasive overactive bladder procedures have risks of complications. The most common side effects of BOTOX® include UTIs (3.6% to 54.5% with four of the RCTs reporting rates of >40.0%), urinary retention (10 studies and ranged from 0% to 43%), the need to perform self-catheterization (20 studies and ranged from 0% to 43% with six studies reporting rates higher than 20.0%, with the need for self-catheterization

persisting for 6-9 months in some patients), and neurological adverse events (AUA/SUFU 2014 OAB Guidelines). Complications with InterStim therapy or sacral nerve modulation include pain at the stimulator site (3.3 to 19.8% of patients), pain at the lead site (4.5 to 19.1% of patients), lead migration (2.2 to 8.6% of patients), infection/irritation (2.2 to 14.30% of patients), electric shock (5.5 to 10.2% of patients) and the need for surgical revision (6.25 to 39.5% of patients, with greater than 30% of patients in most studies) (AUA/SUFU 2014 OAB Guidelines).

Treatment of Stress Urinary Incontinence

Stress urinary incontinence differs from urge incontinence in that it is often more effectively managed with surgical procedures than medications. There are no FDA approved medications that are indicated for the treatment of stress urinary incontinence. Over the years, a variety of surgical techniques have been adopted, each with varying success and complication rates. A very recent study estimates that the lifetime risk of surgery to treat SUI (or POP) in women is 20% by age 80. (Wu et al., Obstet. Gyn., June 14, 2014.)

Since Arnold Kegel first described pelvic floor exercises over 50 year ago, "Kegels", as they are known, have been a mainstay treatment for stress incontinence. Pelvic floor muscle therapy is the process by which someone learns to relax and contract the levator ani or pelvic floor muscles in order to strengthen them. In some cases, the doctor will use biofeedback or electric stimulation to the pelvic floor in order to help the patient better identify these muscles.

Extensive research has been done on the efficacy of pelvic floor exercises, both with and without biofeedback therapy. Many studies have shown that if the woman is diligent, compliant and determined, exercise therapy improves leakage symptoms, as high as 50% in some studies (Berghmans LC et. al., Br. J. Urol, 1998). But as with any exercise program, successful

outcomes require long-term motivation and this is difficult for many people to maintain. There is little doubt that in cases of mild SUI, pelvic floor exercises should be tried. However, there is question whether they are effective for women with more severe leakage symptoms. A recent study in the New England Journal of Medicine (Labrie et al., N. Engl. J. Med. 2013) showed that when women with moderate to severe SUI were randomized to treatment groups for pelvic floor therapy or surgery (midurethral sling insertion), the sling arm had much higher subjective cure (85% vs. 53%) and improvement rates (91% vs. 64.4%).

The use of a bulking agent/injectable is the most minimally invasive procedure for stress incontinence. The clinician will inject a substance underneath the lining of the urethra, usually in an office setting, which causes the lumen of the urethra to tighten and make the bladder less leaky. Agents which have been commonly used are collagen, Coaptite, Durasphere and Macroplastique. Although this is a minimally invasive technique with a low complication rate, the results are often disappointing (25-50% cure or improvement) and the effect is temporary (under 12 months requiring multiple repeat injections). (Gorton E. et al., BJU Int. 1999 Dec; 84(9): 966-71. Periurethral collagen injection: a long-term follow-up study.)

Retropubic suspensions are open procedures which use permanent suture (i.e. Prolene, Gortex, Ethabond) material to attach the endopelvic fascia at the neck of the bladder to the back of the pubic bone or ligament. Traditional Burch colposuspension is a standard approach which requires a wide abdominal incision and is often performed during abdominal surgeries such as hysterectomy and sacrocolpopexy, a surgical procedure used to repair pelvic organ prolapse. The Marshall-Marchetti-Krantz (MMK) is a similar procedure which also requires a wide abdominal incision. Both procedures require a prolonged hospital stay and recovery period. Some newer less invasive procedures use laparoscopy and robotics, which requires small

"keyhole" incisions. Laparoscopy has a faster recovery time and less postoperative pain than the open Burch, but its long-term effectiveness is not yet known.

Research has shown that while open retropubic suspensions are effective treatments for stress urinary incontinence (Lapitan MC, Cody JD. et al. published in the Cochrane database , 2012), in general, there is greater morbidity than more minimally invasive approaches. In addition, there is a greater chance of postoperative de novo pelvic organ prolapse than after slings.

Sling procedures were first introduced in the early 1900s and have undergone multiple modifications since that time. Von Giordano has been credited with performing the first pubovaginal sling operation in 1907. High quality trials have shown as good if not better success rates for the pubovaginal sling procedure when compared to Burch colposuspension. (Albo, M et. al., NEJM 2007; Bandarian, M. et. al., J. Obstet. Gynaecol. 2011; Novara, et al. Eur. Urol. Aug. 2010). The conventional pubovaginal sling procedure involves making a wide incision above the pubic bone to harvest a layer of tissue from the abdominal wall (rectus fascia). Alternatively, a strip of fascia from the outer thigh (fascia lata) is used. Permanent sutures (either Prolene or Ethabond) are sutured to either side or the graft. This tissue strip is set aside and later serves as the sling. The surgeon then makes an incision in the vaginal wall. The piece of tissue is passed under the urethra and bladder neck, somewhat like a hammock, and secured above the abdominal wall by tying the permanent suture to itself. The sling works by compressing and supporting the urethra without being too tense, which can cause urinary obstruction.

As is the case with retropubic suspensions, the autologous fascial sling procedure has the disadvantage of high morbidity with prolonged hospital stay (2-3 days) and often, the need for prolonged postoperative catherization. A randomized controlled study known as the SISTEr trial (Albo, ME et al. NEJM 2007) was a landmark paper comparing retropubic suspensions (Burch colposuspension) to pubovaginal sling (autologous fascia). A total of 655 women were randomly assigned to study groups: 326 to undergo the fascial sling procedure and 329 to undergo the Burch procedure. At 24 months, stress incontinence specific success rates were higher for women who underwent the fascial sling procedure than for those who underwent the Burch procedure (66% vs. 49%, $P<0.001$). However, more women who underwent the fascial sling procedure had urinary tract infections, difficulty voiding, and postoperative urge incontinence.

In order to reduce operative time, recovery time and overall morbidity of the pubovaginal sling procedure, several modifications have evolved which have strived to either eliminate the fascial harvest and/or eliminate the suprapubic incision. Allograft or cadaveric fascia has been used to replace the woman's own tissues. Short term outcomes are similar to autologous fascia, but some studies suggest late failures and histological studies may be a cause for concern for durability. (O'Rielly & Govier, J. Urol. 167:1356, 2002.) Furthermore, little is known about the graft–host relationship and possible mechanisms of graft degradation for cadaveric materials (Woodruff AJ, et al., Urology. 2008.) The risks of disease transmission with these materials remain unknown. Traces of genetic material have been isolated from commercially available cadaveric sling materials although there have been no reports of disease transmission related to cadaveric grafts in the urologic literature

Over the years, physicians have continued to pursue new surgical treatments to combat stress incontinence. The transvaginal bone anchored sling had also been adopted using allograft or xenograft (animal product) with far worse results then the retropubic sling, and has been abandoned. The Raz/Stamey and modified Peyrera needle suspension urethropexies were developed in the early 1990s as minimally invasive procedures for stress incontinence with low morbidity but poor long term outcomes and have since been abandoned.

The Evolution of the Gynecare TVT Sling

Gynecare Retropubic Tension-Free Support for Incontince ("TVT"), the first minimally invasive sling to utilize non-absorbable polypropylene (Ethicon, Somerville, NJ, USA) was introduced to the market in Europe in 1997 and in the U.S. in 1998. TVT revolutionized the treatment of SUI by offering effective and long term management of women's leakage, with results similar to or better than the old standards (Burch and autologous fascial sling), but without significant morbidity. The procedure was originally described by Ulmsten and Petros in 1995 and was based on the 'Integral Theory' whereby reinforcing the pubococcygeal muscles at the level of the mid-urethra corrects the deficient mechanism that causes incontinence. The sling material, PROLENE® mesh, is a synthetic macroporous (>75 microns), polypropylene monofilament knitted mesh (Amid type 1) placed by a retropubic approach.

The original sling procedure was described as appropriate in an outpatient setting under local, light general or regional anesthesia. The woman's legs are placed in stirrups in "lithotomy" position and a Foley catheter is placed in her bladder. A local anesthetic is injected into the vaginal wall at the level of the midurethra and a small (approximately 1.5 cm) incision is made vertically through the epithelial layer of the vagina and into the fascia over the urethra.

Metzenbaum scissors are used to create a tunnel on either side of the urethra. The needle trocar is then passed in a bottom-to-top approach through these tunnels, following the curve of and hugging the pubic bone, exiting the suprapubic skin approximately 2 - 2.5 cm from the midline on each side. Cystourethroscopy is then performed to confirm that the trocars have not perforated the bladder or urethra. Once bladder integrity is confirmed, the needle trocars are pulled up so that the sling, which is covered by a plastic sheath, exits the suprapubic skin. The plastic sheath is cut and the sling is tensioned loosely (over a dilator or clamp), while removing the plastic sheath. This maneuver deploys the sling in the surrounding tissues where it can integrate and provide a scaffold for tissue ingrowth. The vaginal wall and small incisions are closed at the end of the case.

The original TVT used a mesh implant that was mechanically cut, which is still offered today. The mechanically cut mesh induces an initial "Velcro effect" and then tissue ingrowth to anchor in the host tissues within 3–4 weeks after insertion. The use of a permanent, non-absorbable mesh increases the durability of the repair and reduces the chances that urethral support will weaken over time.

As is the case with other types of sling surgery, tensioning of the TVT requires experience and understanding of the tension free technique. Some surgeons use the technique originally described by Ulmsten where the patient is kept awake during the case so she can cough with a full bladder and just enough tension is placed to get the leak to stop. However, over the 17 years that TVT has been on the market, many surgeons have come to prefer placing a dilator or clamp underneath the sling and leave a 1 cm gap between the urethra and the sling. This technique optimizes the probability of the tissue to incorporate into the mesh post operatively without over tightening.

Adjusting the tension on a sling is one of the most critical parts of the procedure, with significant impact on its outcome. Placing the sling on too much tension can result in postoperative voiding complaints – de novo urgency, frequency, urinary retention and/or the need for a sling revision. Using too little tension may result in failure to cure stress incontinence. Moreover, different patients tolerate different amounts of sling tension. Some women may require a tighter sling to stay dry why others will be unable to tolerate any amount of direct tension. While there are understood general principles around tensioning, there is no specific set of 'rules'that will ensure the same results in every case. Often, it is more of an art than an exact science, and the surgeon must rely on his or her training, experience and best judgment to determine how loose or tight to make a sling.

TVT has now been on the market for 17 years and is taught in residencies and fellowships as a matter of course because it is widely recognized as a suitable treatment option for SUI in a broad category of women. Following the introduction of the original TVT, there have been numerous iterations of the TVT sling. Top to bottom, obturator outside-in (Delorme, 2004) and inside-out (de Leval, 2003) techniques were developed over time, addressing surgeon's differing preferences based on various considerations: patient factors, surgeon training and personal experience. In 2006, Ethicon began to offer a version of TVT Retropubic that employed a laser-cut mesh implant.

I have used retropubic TVT and its subsequent iterations for years and have been fortunate to have started my training during a time when these products were available. I cannot imagine what my practice would be like if I could not offer women such a safe and effective treatment for a debilitating condition such as stress incontinence. I have many mentors who talk about what the treatment was like "back in the day." I treat patients who still recall the

debilitating surgery they had 30 years ago which kept them in the hospital for a full week and they could not urinate for three months after. It is such a different experience for my patients, most of whom cannot believe what a positive experience it was and wish they had done it 10 years earlier. They have no idea what their predecessors had to endure.

TVT Retropubic Medical Literature

There has been an extraordinary amount of scientific research conducted on the midurethral sling: a Medline literature search reveals over 2000 publications. The best studied sling is the retropubic TVT with over 100 randomized controlled studies and abstracts. (ETH.MESH.08307644 and 45.) The initial results showed that it was very successful (91% success, as defined by the authors, at 1 year) with a low complication rate. The first long-term data were from Nilsson et al, who reported objective and subjective cure rates of 84.7% with a median follow-up of 56 months. (Nilsson et al., Int. Urog. J. 2001.) Subsequently, Nilsson et al. reported longer follow-up (11 years) in a prospective observational cohort of 90 women. They showed a 90% objective and 77% subjective cure rate with no long-term adverse events. The seventeen year data published in August 2013 was very similar indicating that the retropubic TVT is a time-tested and safe procedure to restore continence to women.

This long term data has been replicated in other series. Svenningsen 2013 reported on 603 women who underwent TVT at 4 different centers in Norway between 1998 and 2000. Of the 603 women, 483 were alive at the time of collection of data, which was collected and stored in the Norwegian National Incontinence Registry Database. The authors reported that over a 10-year period, 3 mesh exposures were diagnosed and surgically managed, and 1 asymptomatic case was identified, resulting in total number of 4 (0.8%) exposures over a decade.

Serati reported on 10 year follow up for 58 women having undergone a TVT for SUI. No patient required sling release during the ten-year observation period. There was not a single patient with significant vaginal, bladder, or urethral erosion, nor did any patient develop de novo dyspareunia during the 10-year follow up. (Serati 2012.)

Heinonen 2012 reported on a 10.5-year study of 138 women who underwent TVT. One patient (0.8%) had a tape erosion in the bladder. Two patients required sling lysis: one patient due to retention at 1 year post-operatively, and another due to pain at 8 years. In both patients, their symptoms resolved after sling incision, and both maintained continence. These findings support my opinions and are consistent with the collective body of literature demonstrating that sling lysis, though not commonly required, is an effective method of addressing late retention.

Aigmueller 2011 is a 10-year TVT study of 141 women who underwent TVT between 1999 and 2001. Two patients underwent reoperation for bladder or urethral erosion (Table 2 [n=141, 2/141 = 1.4%]). There was 1 minor vaginal extrusion at follow up that was treated conservatively (1/117 = 0.8%). This data further supports my opinions and is consistent with my experience. Notably, the data presented by Aigmueller is also consistent with the long-term data reported by Nilsson in the 11 and 17-year TVT studies.

Olsson 2010 is a 10-year TVT study of 124 patients. "One patient had a defect in the healing of the net two months post-operatively [1/124 = 0.8%]." The authors also "did not observe any late tape rejection." Peri-operative bleeding (>100 ml) occurred in 2.7% (4/124), bladder perforation in 2.7% (4/124) and urethral injury in 1.4% (2/124). None of these patients with previous complications had any voiding difficulties at follow-up. Furthermore, the noted complications were easily treatable. For example, bladder perforation is to be recognized during

the operative procedure through cystoscopy and addressed at that time, resulting in no long-term clinical impact.

Liapis 2008 reported on a 7-year TVT study of 61 women. There was one mesh exposure noted at 29 months postoperatively (1/61 = 1.6%). This exposure was treated by cutting the exposed mesh edges in the vagina. The patient remained continent. No other patients had evidence of mesh exposure at the 7-year follow-up.

Novara 2008 was a meta-analysis of 169 studies, 33 of which were RCTs, comparing complications rates of mid-urethral slings to other surgical options for the treatment of SUI. In Table 6 of the article there are over 30 studies specific to the TVT device noted that had 2 years follow-up at the time of the study. Vaginal exposure was only 1.1%. Reoperation was also low at 3.2%.

In a study by Song, et al. presented this year at the 2014 AUA meeting entitled "The long-term outcomes from TVT procedure for female stress urinary incontinence; Data from minimal 13 years of follow-up," 206 women who underwent the TVT procedure for SUI were analyzed for success rates and patient satisfaction. At 13 years after surgery, the overall cure rate was 82.5%, with a satisfaction rate of 67.5% (which correlated with the postoperative presence of frequency, urgency, and urge incontinence and not because of persistent stress urinary incontinence.) Importantly, there was an absence of long-term adverse events secondary to the TVT procedure. At 13-year follow-up, only 3 patients (1.5%) had postoperative complications, including mesh exposure in 1 patient and de novo urgency in 2 patients. The authors concluded that the high success rate both in subjective and objective goal regardless of any independent predictive factors suggested that the TVT procedure is the recommendable method for the

management of female SUI. These studies are further examples of the body of quality data on the retropubic TVT which support its use.

There have also been several studies which have specifically investigated TVT complications. (Kuuva, N et al. Acta Obs Gyn Scand, 2002; Karram, M., Obs. Gyn., 2003; Nguyen, Obgyn 2012.) The data shows that retropubic TVT does not have any higher rate of complication than traditional procedures when looking at complications such as intraoperative bleeding, bladder perforation, and postoperative voiding dysfunction. In fact there is data to suggest that many of these risks may be decreased with TVT. One milestone paper known as the TOMUS trial (Trial on MidUrethtal Slings trial) (Richter, et. al., NEJM 2010) was a well-designed randomized controlled study comparing retropubic and transobturator midurethral slings in 565 women. The authors compared overall success rates of these procedures at 12 months. In a follow up study at 2 years (Albo, ME et al. J. Urol. 2012), they assessed frequency of complications such as urinary tract infection, voiding dysfunction and wound complications requiring and not requiring surgical intervention.

Five year follow up on the TOMUS trial suggested a slight decrease in success for both retropubic and transobturator slings, however, satisfaction remained high in both arms. Women undergoing a transobturator sling procedure reported more sustained improvement in urinary symptoms and sexual function. New mesh erosions occurred in both arms over time, although at a similarly low rate. Women in the retropubic arm had a slightly increased rate of voiding dysfunction (urinary urgency) and a greater negative impact on quality of life as compared to those who had the obturator approach. (Kenton et al., J. Urol 2015.)

Interestingly, these same authors were involved in the SISTEr trial comparing these same parameters in both Burch colposuspension and pubovaginal sling. The data suggests a lower or equivalent incidence for all these categories in the retropubic TVT group. Postoperative UTI has an incidence of 17.1% (n=52) in the TVT group compared to 32% (n=105) and 43% (n=157) in the Burch and PVS groups. Postoperative voiding dysfunction is 3% (n=9) in the TVT group and 0% and 6.1% (n=20) in the Burch and PVS groups. There were 11 wound related complications requiring intervention and 6 not requiring intervention in the TVT group. These numbers compare favorably to 13 surgical and 69 nonsurgical complications in the Burch group; and 11 surgical and 71 non-surgically managed wound complications in the pubovaginal sling group. The Urinary Incontinence Treatment Network also performed a 2 year follow up on this cohort of women and found that with regards to sexual function, there was improvement after TVT and TVT-O. (Zyczynski, H. et al. Am. J. OBGYN 2012.)

Laurikainen et al (2014) presented a 5 year multicenter trial which compared –TVT retropubic to TVT-O The objective cure rate was 84.7% in theTVT group and 86.2% in the TVT-O group, with no statistical difference between the groups. Subjective treatment satisfaction was 94.2% in the TVT group and 91.7% in the TVT-O group, with no difference between groups. Complication rates were low, with no difference between groups. Athanasiou et al (2014) performed a 7 year retrospective study on TVT-O. They reported overall objective and subjective cure rates of 81.5 % (101/124) and 83.5 % (103/124), respectively.

Sexual function after TVT sling insertion has also been studied. Naumann, G. et al. (Arch. Gyn. Obstet. 2013) compared retropubic TVT and sling incision slings in a prospective study looking at quality of life parameters before and after sling procedure using the Female Sexual Function Index (FSFI) questionnaire in sexually active patients. They concluded that both

continence and sexual function satisfaction were significantly improved postoperatively at 6 months in both groups. The Urinary Incontinence Treatment Network which had conducted the TOMUS trial also performed a 2 year follow up on this cohort of women and found that with regards to sexual function, there was improvement after TVT. (Zyczynski, H. et al. Am. J. OBGYN 2012.)

In a meta-analysis by Schimpf et al. (Am. J. Obgyn. 2014), the authors conducted a systematic review including over 100 randomized controlled trials from 1990 through April 2013 with a minimum 12 months of follow-up comparing midurethral sling procedures for SUI to another sling or Burch urethropexy. They looked at long-term adverse events and effectiveness based on objective and subjective cure rates. In this study there was a summary estimate of incidence for dyspareunia of 0% for TVT (0 out of 488 patients) and the authors concluded that "dyspareunia is rare with any type of [MUS] sling. . .." (Schimpf at 71.e16.) Schimpf also reported exposure rates of 1.4% for retropubic slings across 29 studies, and a 1.9% rate of returns to the operating room to treat an erosion across 12 studies. (Schimpf at 71.e7.)

The 2009 Cochrane review on midurethral slings, which included sixty-two trials involving 7,101 women, concluded the following:

- minimally invasive synthetic suburethral sling operations appear to be as effective as traditional suburethral slings (8 trials, n=599, risk ratio (RR) 1.03, 95% confidence interval (CI) 0.94-1.13), but with shorter operating time and less postoperative voiding dysfunction and de novo urgency symptoms;
- minimally invasive synthetic suburethral sling operations appear to be as effective as open retropubic colposuspension (subjective cure rate at 12 months RR 0.96,

95% CI: 0.90-1.03; at 5 years RR 0.91, 95% CI: 0.74-1.12) with fewer perioperative complications, less postoperative voiding dysfunction, shorter operative time, and hospital stay;

- minimally invasive synthetic suburethral sling operations have significantly less de novo urgency and urgency incontinence, shorter operating time, hospital stay, and time to return to daily activities; a retropubic bottom-to-top route is more effective than top-to-bottom route (RR 1.10, 95% CI: 1.01-1.20; RR 1.06, 95% CI: 1.01-1.11) and incurs less voiding dysfunction, bladder perforations, and tape erosions.
- Monofilament tapes such as TVT have significantly higher objective cure rates (RR 1.15, 95% CI: 1.02-1.30) compared to multifilament tapes and fewer tape erosions (1.3% vs. 6% RR 0.25, 95% CI: 0.06-1.00).

(Ogah, J. et al., Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women (Review), Neurourology & Urodynamics 30:284-291 (2011), summary of 2009 Review.) The Cochrane Review compared the rates of several potential complications such as bladder perforation, de novo urgency and perioperative complications such as hematoma formation. The authors concluded that the current evidence base suggests that minimally invasive synthetic suburethral slings are as effective as traditional slings and open retropubic colposuspension, but with less postoperative complications.

In an update to the original Cochrane Review, released in 2015, the authors analyzed 81 trials that evaluated 12,113 women. Ford AA, Rogerson L, Cody JD, Ogah J. Mid-urethral sling operations for stress urinary incontinence in women. *Cochrane Database of Systematic Reviews* 2015, Issue 7. Art. No.: CD006375. DOI: 10.1002/ 14651858.CD006375.pub3. (July 1, 2015).

The 81 trials, which included 12,113 patients through June 2014,demonstrated that "over 80% of women with stress urinary incontinence are cured, or have significant improvement in their symptoms, with either operation [retropubic or obturator sling], for up to five years after surgery.... [T]he information that is available for quality of life shows that it improves as a result of these operations, though there is no clear difference between the two procedures." The studies show that slings which pass through the retropubic space have a slightly higher risk of bladder perforation and bladder dysfunction, but a lower rate of postoperative groin pain than transobturator procedures. In addition, there is some evidence to suggest that there is a decrease in the need to return to the operating room for repeat incontinence surgery in the long term (greater than 5 years) after the retropubic approach. (Ford 2015.)

The Ford 2015 Cochrane Review supports clearly that TVT slings, "have been the most extensively researched surgical treatment for stress urinary incontinence (SUI) in women and have a good safety profile. Irrespective of the routes traversed, they are highly effective in the short and medium term, and accruing evidence demonstrates their effectiveness in the long term. This review illustrates their positive impact on improving the quality of life of women with SUI." In addressing the potential risks of midurethral slings, the authors stated that "tapes passing behind the pubic bone (retropubic) seem to carry a greater risk of injuring the bladder during the operation and of women experiencing problems emptying their bladder completely after surgery. However, this operation leads to less groin pain in the short term. There is some limited evidence that this way of inserting the tape has a lower risk of requiring a repeat operation in the long term compared to tapes passing through the groin (transobturator). There is moderate quality evidence that overall reported rates of tape-related complications are low, such as erosion of the tape into the vagina at about 2% for both routes of tape insertion. Further,

"reported occurrence of problems with sexual intercourse including pain was low, and leakage of urine during intercourse are improved following insertion of these tapes." (Ford 2015.)

Tommaselli performed a meta-analysis of medium and long term data on synthetic slings. There were 11 RCTs [14–24] and 38 nonrandomized studies, including prospective, retrospective, and cohort studies [25–62] with a total of 6,406 patients. The authors looked at objective and subjective cure rates as well as long term complications. Retropubic midurethral slings (RP-MUS) had similar objective cure rates (OR 1.15, 95 % CI 0.75 – 1.76) but higher subjective cure rates than transobturator midurethral slings (TO-MUS) (OR 1.76, 95 % CI 1.08 – 2.86), although one study found similar subjective cure rates as between RP-MUS and TVT-O specifically (OR 0.92, 95% CI 0.47-1.80). Bladder injuries were more frequent (OR 7.01, 95 % CI 2.94 – 17.90) and vaginal erosions were less frequent for RP-MUS (OR 0.24, 95 % CI 0.07 – 0.84). Pain-related complications were more common with TO-MUS than with minimally invasive tapes (OR 8.75; 95 % CI 9.02 – 5). The authors concluded that "RPMUS and TO-MUS have similar objective cure rates in the long-term and medium-term but TOTs have a lower subjective cure rate than TVT. This efficacy is backed by a high safety profile, and by a limited number of complications which were seldom severe."

The Gold Standard

Numerous investigators and societies have concluded – and I agree – that the synthetic midurethral sling is the gold-standard treatment for women with stress incontinence based on, among other reasons, large meta-analyses of the data showing equal/better outcomes and decreased morbidity compared to older procedures. (Cox, et al. Nature Reviews, 2013; Novara et al. Europ. Urol. 2010).

In 2009, a panel of experts developed the American Urological Association (AUA) guidelines for the urologist treating stress incontinence in the "index patient" – the otherwise healthy female who elects surgical correction for her stress incontinence. The guidelines were based on a total of 436 articles which were suitable for inclusion in the meta–analysis. They looked at outcomes and complications for multiple types of anti-incontinence procedures. In this exhaustive analysis, it was shown that complications are possible in any given procedure. The complications associated with slings of any type are bladder perforation, voiding dysfunction and UTI. In the case of TVT, there is an added complication of mesh exposure. The panel agreed that this is the only complication that is unique to the midurethral sling procedure.

Their conclusions were as follows:

1. In this meta–analysis, the midurethral slings had an efficacy comparable to autologous slings in the surgical treatment of SUI.
2. Several "versions" of the midurethral sling procedures do not have similar long–term efficacy data.
3. There are complications that may occur that are unique to specific mesh materials; however, these complications appear to be infrequent. Intraoperative use of cystoscopy can be performed to minimize the risk of urinary tract injury or erosion.
4. The midurethral sling is an alternative in the management of SUI. The incidence and implications of these complications along with the more rapid recovery and more efficient return to normal voiding after surgery should be discussed with patients before surgery.

(Dmochowski, R.R., J. Urol. 2010 May; 183(5):1906-14. Update of AUA guideline on the surgical management of female stress urinary incontinence.)

The AUA released a Position Statement in November 2011 on the use of vaginal mesh for the surgical treatment of SUI. The statement noted that the efficacy of synthetic polypropylene mesh slings is equivalent or superior to other surgical techniques, based on Level

1 evidence, with a follow-up to 10 years, and these are not associated with a significant increase in adverse events. The AUA agreed with the FDA recommendation included in its 2008 Public Health Notification of including a comprehensive informed consent before synthetic sling surgery, disclosing all possible risks and adverse events. Additional recommendations included not only rigorous urological training in pelvic anatomy and pelvic surgery, and intraoperative cystoscopy to exclude urinary tract injury, but specific surgical expertise on 'specific sling techniques' as well as the diagnosis and treatment of related complications. The statement concluded that 'synthetic slings are an appropriate treatment choice of women with stress incontinence, with similar efficacy but less morbidity than conventional nonmesh techniques'.

In January 2014, the American Urogynecological Society (AUGS) and the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) released a joint position statement on the use of polypropylene mesh midurethral slings. These nationally and internationally recognized societies are comprised of leaders in the fields of both urology and gynecology, with subspecialty training in FPMRS. Their position statement stated, among other things, that:

1. Polypropylene material is safe and effective as a surgical implant.

2. The monofilament polypropylene mesh MUS is the most extensively studied antiincontinence procedure in history.

3. Polypropylene mesh midurethral slings are the standard of care for the surgical treatment of SUI and represent a great advance in the treatment of this condition for our patients.

4. The FDA has clearly stated that the polypropylene MUS is safe and effective in the treatment of SUI.

They concluded, in pertinent part:

"The polypropylene midurethral sling has helped millions of women with SUI regain control of their lives by undergoing a simple outpatient procedure that allows them to return to daily life very quickly. With its acknowledged safety and efficacy it has created an environment for a much larger number of women to have access to treatment. In the past, concerns over failure and invasiveness of surgery caused a substantial percent of incontinent women to live without treatment. . . .. This procedure is probably the most important advancement in the treatment of stress urinary incontinence in the last 50 years and has the full support of our organizations which are dedicated to improving the lives of women with urinary incontinence."

I have also reviewed the November 2015 Joint Practice Bulletin issued by ACOG and AUGS regarding Urinary Incontinence in Women. In particular, this Bulletin states, among other things, that:

The following conclusions and recommendations are based on good and consistent scientific evidence (Level A)….:

- Synthetic midurethral slings demonstrate efficacy that is similar to traditional suburethral fascial slings, open colposuspension, and laparascopic colposuspension. Compared with suburethral fascial slings, fewer adverse events have been reported with synthetic midurethral slings. Voiding dysfunction is more common with open colposuspension than with synthetic midurethral slings.

- There are substantial safety and efficacy data that support the role of synthetic mesh midurethral slings as a primary surgical treatment option for stress urinary incontinence in women.

I agree with and support each of these position statements. As a member of these medical organizations, I am proud that we have the courage as a medical community to let our voices be heard to support the availability and appropriate use of mid-urethral slings such as TVT.

Known Risks of All Incontinence Surgeries

There are several complications of any anti-incontinence surgery which are, through clinical experience and reporting in literature, well known to surgeons who routinely perform these procedures and are learned in the course of their training. These procedures carry a risk of damage to the surrounding nerves or vessels which can result in internal sphincter deficiency or hemorrhage. There is the possibility of retropubic bleeding; the space of Retzius or retropubic space is an area with a rich venous plexus which can be inadvertently disrupted causing significant bleeding which may be difficult to control. Injury to the lower urinary tract (ureter, bladder or urethra) in the course of dissection has been reported. Bowel injury is a rare but reported complication. Difficulty urinating from surgical overcorrection either from a sling or retropubic suspension may require additional surgery to release the obstruction. De novo urgency incontinence (UUI not present prior to surgery) and overactive bladder, wound complications, poor wound healing, and adhesions or scar formation are well described. Additional complications include infection (urinary tract and wound), pelvic pain and pain at the

surgical site, painful intercourse and the formation of fistulas (holes that form from the urinary tract to the vagina causing continuous incontinence).

Management of Mesh Exposures Following Sling Placement

In 2011, in order to standardize definitions, the International Continence Society (ICS) and International Urogynecologic Association (IUGA) created definitions for graft complications. The term "exposure" is defined as the presence of graft material in the wall of the vagina. An equivalent term is extrusion. In contrast, the term "perforation" or "erosion" implies that the graft has entered a visceral cavity such as the bowel or urinary tract. In the past the term erosion was used synonymously with exposure. True mesh erosion (into a visceral cavity) is extremely rare (<1%). (Kuuva, et al Acta Obstet Gynecol Scand. 2002 Jan;81(1):72-7. A nationwide analysis of complications associated with the tension-free vaginal tape (TVT) procedure.)

Mesh exposure is a known complication of TVT and other types of synthetic midurethal slings with incidence in the literature typically between 0 to 7%. (AUA Guidelines, Dmochowski, R., J. Urol. 2010). In their recent meta-analysis, Schimpf et al. reported 1.4 % exposure of retropubic slings across 29 studies (5684 patients). (Schimpf et al. 2014.) Sometimes exposures happen due to technical error. The graft needs to be placed deeply under the vaginal wall in the true preurethral space without "splitting the fascia" in the dissection. Otherwise the tissue over the sling is too thin to promote adequate healing. Furthermore if there is a "buttonhole" or direct passage of the trocar through the vaginal wall, it needs to be recognized or the mesh will be placed directly into the vaginal cavity, usually through a lateral sulcus. Non-technical or patient factors for exposure include poorly controlled diabetes, steroid

use, smoking history, multiple previous surgeries with significant scar tissue and age or decreased vaginal wall estrogenization. In these cases, the exposure is usually noted at the site of the vaginal incision. Sometimes, an exposure happens because the patient does something too strenuous in the immediate post-operative period, or returned to sexual activity too quickly, causing breakdown of the vaginal incision and subsequent mesh exposure. This is literally the case of "popping a stitch." Some authors have advocated that hematoma present under the vaginal wall contributes to poor wound healing and subsequent mesh exposure. (Frankman, EA Obstetrics and Gynecology International Volume 2013). These factors are all relate to principles of wound healing and fall into the category of wound healing complications.

Although mesh exposure is not a complication seen in traditional surgeries that do not employ a sling, other types of graft materials used in sling surgery do present a risk of exposure. Allografts and biologic materials have been shown to have equivalent rates of exposure to mesh (Drake et al, Urogyn J Pelvic Floor Dys. 2005; Flynn MK, AM J Obs Gyn, 2005). In most cases, allograft extrusions are managed nonsurgically.

The management of mesh exposure is dependent on many different factors: the patient's age and comorbidities, the size and location of the exposure, the patient's symptoms and whether or not she is sexually active. Hammad et al. (Australasian survey. Eur Urol 2005) reported that 35% of vaginal erosions were asymptomatic and the exposure was discovered on routine follow-up. Kobashi et al. presented consistent data in a study of > 90 women who received a polypropylene mesh for the treatment of SUI; 3 developed vaginal exposure, but only 1 had symptoms such as pain or discomfort during sexual activity. (J. Urol. 2003;169:2242–3.) In my own practice, I have had similar findings.

While several authors have reported on their experience with mesh exposure, there is currently no evidence-based consensus on exactly how to manage exposures. That said, it is widely practiced and believed that, in general, small asymptomatic exposures can usually be successfully managed conservatively with pelvic rest and localized estrogen cream, or in-office excision. Larger and symptomatic exposures may require surgical excision (either partial or complete) to remove the exposed implant. Once adequate vaginal flaps have been created, the vaginal wall is closed with absorbable suture. In reviewing the literature the risk of reoperation after such a procedure for mesh extrusion is extremely low, although reoperation due to recurrent stress incontinence is documented. (Viereck et al., Int. Urogyn. J., 2013; Clifton et al., J. Urol. 191: 710–14, March 2014.)

Removal of mesh for the treatment of exposure is, in most cases, a successful practice and the risk of reoperation after such a procedure is low. This is further illustrated by the table set forth below:

META-ANALYSIS	NUMBER OF EVENTS/TOTAL PATIENTS	EXPOSURE RATE	REOPERATION RATE
Ford 2015	21/1000	2%	1.6-2.4%
Tommaselli 2015	3801	2.1%	
Schimpf 2014	84/5684	1.4%	1.9% (for exposure) (13/703 patients)
Ogah 2011	2/153 and 8/249	1.3%-3%	1.6% - 2.4% (related to tape insertion or postop voiding dysfunction)
Novara 2008	4764 (Table 6)	1.1% overall	3.2% overall

Overall the reliable scientific literature demonstrates that the rates of reoperation after TVT are in the low single digit range. (Welk B. et al., Removal or Revision of Vaginal Mesh Used for the Treatment of Stress Urinary Incontinence. JAMA Surg. 2015 Sep; 9:1-9; Unger CA et al., Indications and risk factors for midurethral sling revision. Int. Urogyn. J. 2015 Jul 2. [Epub ahead of print] PubMed PMID: 26134541; Jonsson Funk M, et al., Sling revision/removal for mesh erosion and urinary retention: long-term risk and predictors. Am J Obstet Gynecol. 2013 Jan; 208(1):73.e1-7; Schimpf et al., Society of Gynecologic Surgeons Systematic Review Group. Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. Am J Obstet Gynecol. 2014 Jul; 211(1):71.e1-71; Laurikainen E. et al., Five-year results of a randomized trial comparing retropubic and transobturator midurethral slings for stress incontinence. Eur Urol. 2014 Jun;65(6):1109-14; Serati M, et al., Tension-free vaginal tape for the treatment of urodynamic stress incontinence: efficacy and adverse effects at 10-year follow-up. Eur Urol. 2012 May;61(5):939-46; Nguyen JN, et al., Perioperative complications and reoperations after incontinence and prolapse surgeries using prosthetic implants. Obstet Gynecol. 2012 Mar;119(3):539-46; Novara G, et al., Complication rates of tension-free midurethral slings in the treatment of female stress urinary incontinence: a systematic review and meta-analysis of randomized controlled trials comparing tension-free midurethral tapes to other surgical procedures and different devices. Eur. Urol. 2008 Feb;53(2):288-308.) This is also consistent with the extensive experience I have had with midurethral slings in my practice and training.

Material Properties of Synthetic Mesh

Synthetic meshes have different properties. They can be absorbable or non-absorbable. Absorbable meshes are tolerated well in the body but have the disadvantage of less tensile strength. Furthermore, the scar tissue which forms when they dissolve is not as strong as the

reinforced tissue, making them less desirable for use in stress incontinence surgery. Mesh can be microporous <10μm or macroporous >75μm. (Amid, PK Classification of biomaterials and there related complications in abdominal wall hernia surgery. Hernia, 1997). It can be monofilament or multifilament. A mesh pore size of 75μm or greater is necessary to allow macrophages and fibroblasts to enter freely to eradicate bacteria (White, TA ASAIO J.,1988). Lastly, multifilament (braided) have small interstices that are more likely to promote infection than monofilament meshes.

TVT is made of type 1 non-absorbable synthetic mesh – it is macroporous (1.5 mm) and monofilament (polypropylene) making it an excellent sling material. (Gomelsky A, Dmochowski R., J. Urol. 178:4, 1171–1181, October 2007.) Based on my clinical experience and review of the clinical experience of numerous others in the medical literature, the pore size of TVT mesh is entirely appropriate to promote healthy tissue integration. If it were not, we would be seeing failure, rejection and complications on a far grander scale. In fact, the AUGS/SUFU January 2014 Position Statement referenced above cites the Nilsson 17-year TVT data for the proposition that "As a knitted implant for the surgical treatment of SUI, macroporous, monofilament light-weight polypropylene has demonstrated long term durability, safety and efficacy up to 17 years." The question of whether the pore size changes after implantation is also of no clinical significance. TVT does not demonstrate a higher rate of infection or extrusion than any other implanted material, which would be a consequence of deceased pore size or microporous mesh were it to have a clinical impact.

In fact, one of the advantages of TVT is its low infection rate. Although infection is a known risk when using any implant, the medical literature on polypropylene mid-urethral slings shows an extremely low rate of infection. In fact, the large meta-analyses report little to no

infection with synthetic mid-urethral slings. (Ogah et al. (2011)); Dmochowski, R., J Urol. 2010; Schimpf et al. 2014).) That is very consistent with my personal experience in my practice; I rarely if ever have to treat my patients postoperatively with antibiotics to treat a sling infection. Urinary tract infections may develop postoperatively, but not with any greater degree than traditional repairs as evidenced in the TOMUS and SISTre trials. Explanted meshes are by definition "infected" if they have been exposed to the vaginal milieu. But even this situation has questionable clinical significance as patients with TVT mesh exposures do not mount a classic "infection" response such as fever or purulent drainage. In any event, the TVT IFU explicitly warns surgeons of the risk of infection potentiation, inflammation, and extrusion, which would be the indicators that a mesh is being rejected by the patient.

Plaintiffs' experts offer several opinions regarding so-called particle loss and fraying of mechanical cut mesh, degradation, chronic foreign body reaction, excessive contraction, roping, curling and other issues that they contend make PROLENE® mesh unsuitable to treat SUI in women. As a clinician with experience placing over 1500 slings, the overwhelming majority of which are Gynecare mesh slings, treating patients post-operatively, and based on my review of medical literature and training, I must disagree. My experience and the experience of countless other surgeons as reflected the wide body of medical literature on TVT and other polypropylene mid-urethral slings do not suggest that these factors, if they exist, manifest in clinical significance for patients, and certainly not on any widespread basis. If they did, we would not see the levels of safety and effectiveness in TVT slings in the medical literature that make them the procedure of choice for myself and so many of my colleagues.

Regarding claims of "particle loss" and "fraying" with mechanical cut mesh, there is no evidence in the medical literature whatsoever to suggest that slings using laser cut mesh are safer

than slings using mechanical cut mesh, or vice versa. Whether to use mechanical cut mesh or laser cut mesh is solely a matter of surgeon preference, and Ethicon appropriately offers both versions to meet that surgeon preference.

Furthermore, the overall extensive body of clinical data for Gynecare TVT does not support the conclusion that PROLENE® mesh degrades in the body in any manner that has a clinical impact on patients. Clavé et al. (2010) studied how polypropylene mesh which was explanted due to erosion or infection was altered from its pre-implant state. The authors used histologic, chemical analysis, infrared spectroscopy and differential scanning calorimetry. Monofilament polypropylene products had less surface cracking (which they reported was degradation) than multifilament products. Clavé et al. noted that despite exhaustive testing, they could not explain their findings. They stated, "Several hypotheses concerning the degradation of the PP are described. None of these, particularly direct oxidation, could be confirmed in this study." The authors conceded that a weakness of the study was that there was no opportunity to compare explanted mesh from uncomplicated procedures with explanted mesh from the complicated procedures which makes it difficult to conclude if there would also be alterations in products which had not eroded or become infected. Given these limitations recognized even by the study's authors, it cannot be concluded to a reasonable degree of medical certainty or probability that mesh degradation happens in a clinically significant way. This issue has also been evaluated by medical societies AUGS and SUFU which have concluded that the clinical data do not support the extrapolation of reported "surface cracking" in a minority of the Clave samples to degradation. (AUGS-SUFU Frequently Asked Questions by Providers: Mid-urethral slings for Stress Urinary Incontinence. March 2014).

Alternatively, Woodruff et al. (2008) performed histopathologic analysis on 24 explants at 2-34 months after implantation. The indications for removal were not mesh exposure or infection but rather a lack of sling efficacy in 2, urinary retention in 9, and sling obstruction in 13. The types of graft materials were polypropylene mesh (PPM) in 10, autologous fascia in 5, porcine dermis in 4, cadaveric dermis in 3, and cadaveric fascia in 2. No graft degradation had occurred in PPM material. Interestingly, autologous and cadaveric fascia had the most demonstrable graft degradation. The fact that numerous studies on TVT have proven its durability and safety up to seventeen years post implant does not support short or long term degradation. If it did degrade in a clinically significant way, surgeons would see far lower levels of durability in their TVT and TVT-O repairs, and that is certainly not something that I have seen in my clinical practice over many years, nor is that consistent with the reliable scientific studies in women implanted with TVT. Nor does the notion that PROLENE® degrades in the human body make sense given that PROLENE® sutures have been successfully used in vaginal surgery for decades.

Nor does the medical literature provide evidence that the use of TVT results in excessive contraction of tissues causing complications to the patient. To the contrary, Dietz et al. report that based upon ultrasound imaging, the TVT does not seem to contract or shorten over a median observation period of 1.6 years: "Over the observed period between 6 weeks and 3.3 years after TVT placement, our data do not provide any evidence for contraction or shortening of the TVT." Dietz et al., Am. J. Obstet. Gynecol. 2003, 188:950-953. Similarly, in the 17 year follow up performed by Nilsson et al. (2013), the authors reported that there seemed to be no shrinkage of the TVT mesh over time.

Finally, in my experience of over 1500 mesh slings, I have not seen a sling rope or curl in the human body unless an unnecessary amount of tension is placed on the implant causing it to deform. The TVT IFU is clear in stating that the tape should be placed at the midurethra without tension, and that surgeons should be trained in implanting TVT before using it.

Alternative Meshes

Based on my experience and my review of the medical literature, I am not aware of any design or material of mid-urethral sling that does not pose the potential risks of the TVT device, including the risk of exposure, which may require revision. Nor am I aware of any surgery to treat SUI that does not come with a possible risk of urge incontinence, urgency, frequency, or corrective surgery that would create additional scarring. The medical literature shows a risk of exposure from the use of any sling, and the risk of wound complications from any surgery to treat SUI, some of which will require surgical treatment. (Dmochowski RR, et al., Female Stress Urinary Incontinence Update Panel of the American Urological Association Education and Research, Inc, Whetter LE. Update of AUA guideline on the surgical management of female stress urinary incontinence. J Urol. 2010 May;183(5):1906-14; revised 2012 https://www.auanet.org/common/pdf/education/clinical-guidance/Incontinence.pdf; Schimpf et al., Society of Gynecologic Surgeons Systematic Review Group. Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. Am J Obstet Gynecol. 2014 Jul;211(1):71.e1-71.e27.) Still, the reoperation rates in the large systematic reviews such as Ford (1.6% to 2.4%).and Schimpf (1.9%) are acceptably low The macroporous TVT PROLENE polypropylene mesh is the most studied mesh in the world for the surgical treatment of SUI and has the highest degree of biocompatibility when used in the application. (Ford 2015; AUGS-SUFU Frequently Asked Questions by Providers: Mid-urethral slings for Stress Urinary

Incontinence. March 2014; Ogah J, Cody DJ, Rogerson L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women: a short version Cochrane review. Neurourol Urodyn. 2011 Mar;30(3):284-91.)

Alternative meshes such as Gynemesh PS and UltraPro have not been studied nearly to the extent as TVT for the treatment of SUI. Unlike TVT, they are not recommended as a treatment of SUI by the pertinent medical societies. I have not found credible evidence in the medical literature that the use of Gynemesh PS, UltraPro, or laser cut PROLENE Mesh, eliminates (or even reduces) the possible risks of exposure, the need for revisions, or the risk of postoperative incontinence or voiding symptoms. In Okulu 2013, the rate of exposure with Gynemesh PS and UltraPro was equivalent to or greater than the exposure rates typically reported for TVT PROLENE mesh, and was based on a small patient groups. (Okulu 2013; see Novara 2008, Table 6, listing several TVT studies with 24 month follow listing vaginal exposure rates between 1 and 2%.) The Okulu article also involved a different surgical procedure, different shape of mesh, and TVT PROLENE mesh was not a comparator. (Okulu 2013.) Also, when Gynemesh PS and UltraPro are used in a different vaginal indication, to treat prolapse, they do carry risks of exposure and dyspareunia. (See Milani 2012, reporting 14.8% exposure and 9% dyspareunia following use of UltraPro to treat prolapse.)

Summary of Opinions

For the reasons set forth above, it is my opinion to a reasonable degree of medical certainty that:

1. The Gynecare TVT is a safe and effective product that is supported by an extraordinary amount of clinical data. It is indeed the "gold standard" in the treatment of SUI, and an appropriate treatment option for many women who suffer with this difficult and embarrassing condition. From my perspective as a fellowship-trained surgeon who has implanted over 1000 mesh slings over many years, TVT's benefits far exceed its risks for many women and it is not defectively designed;

2. The PROLENE® mesh tape used in TVT is an appropriate, effective and safe material for use in this indication. Polypropylene mesh and sutures have been used an implant for decades. The pore size of the mesh tape in TVT is sufficiently large to allow for proper tissue ingrowth, and has not presented risks of infection, particularly in relation to other implants.

3. The overall and extensive body of clinical data for TVT does not support the conclusion that PROLENE® mesh degrades in the body in any manner that has a clinical impact on patients. If it did degrade in a clinically significant way, surgeons would see far lower levels of durability in their TVT repairs, and that is certainly not something that I have seen in my clinical practice over many years.

4. The safety and efficacy of PROLENE® mesh as an SUI sling does not depend on whether it is mechanically or laser cut. Whether to use mechanically cut or laser cut mesh tapes is a matter of surgeon preference and for that reason, it is appropriate that Ethicon sells both

options. There is no clinical evidence in the medical literature that particle loss, to the extent that it occurs with mechanically cut mesh, has any clinical significance to the patient. There is also no body of clinical evidence demonstrating that laser cut mesh or the other materials proposed by Dr. Rosenzweig have a better safety profile for the patient than mechanical cut PROLENE® mesh to treat SUI.

5. The possible risks of TVT are adequately described in the TVT IFU and in Ethicon's professional education materials associated with TVT. The IFU and the professional education materials appropriately take into account the foundational level knowledge of the trained surgeon who is using the product, as is specifically stated in the TVT IFU.

6. Based on the credible scientific evidence, there is no alternative device that has been demonstrated to reduce or eliminate the risks of TVT.

Expert Rates

My work on this matter has been or will be billed as follows: $500 per hour for records review, preparation of Expert Reports, and consultation; $4000 per half day of deposition or trial testimony; and $7500 for full day of deposition or trial testimony.

Consulting with Ethicon

Based on Ethicon's records, I have preceptored about five events for Ethicon between 2008 and 2011, in which I trained other doctors in the safe and effective use of Prolift and TVT products. I have also participated in design validation activities relating to Gynecare Gynemesh M, which included review and analysis of the proposed IFU for that product. For my services, I was compensated a total of about $10,000.

DATED: February 8, 2016

MD

Nicole B. Fleischmann, MD